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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,309	WELCH ET AL.	
	Examin r	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10.03.2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3 and 5-11* is/are rejected.

7)☐ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-11, filed September 1, 2003 is acknowledged.

Traversal on the grounds that all claims of the present application could be examined together without placing any serious burden on USPTO, since they are closely related to one another and that for efficiency they should be examined in a single application

This is not found persuasive because depending upon the restricted group (I or II) being examined, additional classes/subclasses have to be searched, as explaine in the previous Office Action. Clear distinction have also been made between Groups V & VI, for example, classified in the same class/subclass. This additional searching as explained before would therefore involve undue burden to the Examiner. The requirement is still deemed proper and is therefore made FINAL.

2. **Claims withdrawn** :

Claims 12-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in the above cited response to the restriction requirement.

3. Claims 1-11 are pending and under consideration in this examination.

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. ***Claim Rejections - 35 U.S.C. § 112*** (first paragraph)

Enablement

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide of SEQ ID NO: 2 or specific residues of SEQ ID NO : 2 [**24-886** or **434-444** or... 408-448, etc. as recited in the claims] having the ability to bind and cleave C1-esterase inhibitor, does not reasonably provide enablement for any isolated polypeptide comprising a sequence having at least 70% amino acid identity to the amino acid residues 24-886 (i.e., 30 substitution, deletion or insertions per 100 amino acids). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 5 encompasses any polypeptide, which by definition is modified by substitution, deletion or insertion comprise creating a variant polypeptide(s). The scope of the claims do not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID

NO : 2 or that the SEQ ID NO : 2 comprising the specific residues having the ability to bind and cleave C1-esterase inhibitor.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification.

The specification does not support the broad scope of the claims which encompass numerous modifications (30%), because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the ability of SEQ ID NO : 2 to bind and cleave C1-esterase inhibitor; (B) the general tolerance of SEQ ID NO : 2 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying SEQ ID NO : 2 amino acid residues to the extent claimed with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polypeptide having the ability to bind and cleave C1-esterase inhibitor with a number of modifications in the structure of SEQ

ID NO : 2 and be able to express a viable and functional protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variously modified polypeptides having the ability to bind and cleave C1-esterase inhibitor is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

6. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1-3 & 6-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-3 & 6-11 encompass specific fragments of SEQ ID NO : 2 with no associated function.

The specification, however, only provides a single representative species of the genus comprising SEQ ID NO : 2, having the desired ability to bind and cleave C1-esterase inhibitor. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species of specific fragments of SEQ ID NO : 2, where such fragments of specific amino acid residues (for example, 230-630; claims 1-3 & 9-11) or fragments of 17, 25 or 40 consecutives amino acid residues (claims 6-8) have the desired ability to bind and cleave C1-esterase inhibitor, and for which for which no predictability of structure/activity is apparent. Given this lack

of additional representative species, such as the modifications in order to crate a variant, fragment or derivative of the Formula and still have some activity and/or utility, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Therefore, the written description requirement is not satisfied.

7. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3 & 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Makino et al. [DNA Research 5 : 1-9, (1998)] or Burland et al. [Nucleic acid Research, 26 : 4196-4204, (1998), *see* 1449 (ref : AJ)]. Makino et al. or Burland et al. disclose a polypeptide sequence (Accession No. T42131; T00210) that is 100% identical to SEQ ID NO : 2, or comprises the polypeptide residues or fragments of claims 1-3 & 6-11. The reference anticipates the claims (see the enclosed sequence search alignment, and the cited reference of Makino et al.).

8. Claims 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Brunder (Accession No. Q9ZAL1, May 1, 1999, see 1449 (Ref : AS). Brunder teaches a

polypeptide sequence, Accession No. Q9ZAL1) , wherein 275 consecutive amino acid residue match with Applicant's SEQ ID NO : 2. This polypeptide sequence comprises any fragments having 17, 25 or 40 consecutive amino acids of claims 6-8. The reference anticipates the claims (see the enclosed sequence search alignment between Q9ZAL1 and SEQ ID NO : 2 (residue 24-886).

9. Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. ***Allowable Subject matter***

Claims drawn to 'sequence(s) of SEQ ID NO : 2 having the ability to bind and cleave C1-esterase inhibitor' – which recite both structure and function, have been found unobvious over the cited prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
October 14, 2003